Can immature granulocytes predict mortality in coronavirus disease 2019 (COVID-19) infection in patients with chronic kidney disease?

Immature granulocytes in coronavirus disease 2019 (COVID-19)

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Abstract

Aim: The association between mortality and comorbid diseases such as cardiovascular disease, chronic kidney disease (CKD), diabetes, and other chronic diseases has been reported in COVID-19 patients. Mortality is 14-16 times higher in patients with CKD. Inflammation plays an important role in the pathophysiology of COVID-19. Immature granulocytes (IG%) are used to make an immediate diagnosis in cases of severe infections. Therefore, we aimed to investigate whether IG% can be used as a prognostic factor in CKD patients who have contracted COVID-19.

Material and Methods: All CKD patients admitted to our center in the period between June and December 2020 with a COVID-19 diagnosis were reviewed. Complete blood count and biochemical tests were performed and the results were recorded. According to the occurrence of in-hospital mortality, the patients were categorized into groups and intergroup comparisons were conducted.

Results: Our study included 87 patients, 42 (48.3%) of whom were women. The mean age of the patients was 67.07±13.52 years. Of the patients included in the study, 71 (81.6%) were survivors and 16 (18.4%) were non-survivors. The comparison of the mean IG% between the survivor and non-survivor groups did not reveal a significant correlation (0.72±0.52 vs. 0.71±0.42; p=0.754). The comparison of disease severity between the groups with high and normal IG% did not reveal a significant difference (24.4% vs. 21.1%; p=0.769).

Discussion: IG% cannot be used as an indicator to predict mortality in CKD patients with COVID-19.

Keywords

Coronavirus Disease 2019, Chronic Kidney Disease, Mortality, Immature Granulocytes

Introduction

The novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), first occurred in Wuhan in China at the end of 2019 and caused a global outbreak resulting in seriously devastating socioeconomic effects all over the world [1]. According to the World Health Organization, more than 115 million people have been diagnosed with COVID-19 and more than 2.5 million have died worldwide [2]. While most patients experience mild symptoms such as fever and dry cough, some may quickly develop shortness of breath or even acute respiratory distress syndrome (ARDS) resulting in death [3]. Studies have shown the relationship between mortality and comorbid diseases such as cardiovascular disease, chronic kidney disease (CKD), diabetes, and other chronic diseases in COVID-19 patients. Mortality is 14-16 times higher in patients with CKD [4].

Inflammation plays an important role in the pathophysiology of COVID-19. It is critical to identify potential risk factors to predict COVID-19 patients who will likely develop critical conditions [5]. Recent studies have shown that the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and interleukin-6 (IL-6) as inflammatory markers may be independent risk factors for death in COVID-19 patients [3, 6]. Immature granulocytes (IG%) are indicative of increased myeloid cell production and are used to make an immediate diagnosis in cases of severe infections [7, 8]. Recent studies have reported the role of IG% as a predictor of the severity and complications of gastrointestinal system diseases, sepsis, and cardiovascular system diseases [8-10]. To our knowledge, the benefits of using IG% to predict mortality in COVID-19 patients with CKD have not yet been studied. Therefore, we aimed to investigate whether IG% can be used as a prognostic factor in CKD patients who have contracted COVID-19.

Material and Methods

This is a retrospective observational study conducted at a single center. The study was approved by the ethics committee of our institution with decision number 19/12 and study registration number 2020-362 on December 10, 2020. Data of all patients recorded in the hospital information system were retrospectively reviewed. The patient population consisted of CKD patients who were admitted to a tertiary emergency department and the pandemic triage system due to the presence of COVID-19 symptoms and who received a confirmed diagnosis of COVID-19 from among patients with suspected clinical, laboratory, and radiological findings for COVID-19.

Sample selection was not performed. Instead, all CKD patients admitted to our center in the period between June 1 and December 1, 2020, who received a COVID-19 diagnosis were reviewed. The quantitative reverse transcription-polymerase chain reaction test (RT-PCR) was performed with samples taken from the upper respiratory tract (nasopharyngeal and oropharyngeal secretions) to make the diagnosis of COVID-19. In accordance with the guidance provided in the Republic of Turkey Ministry of Health's COVID-19 diagnostic and therapeutic guidelines, the RT-PCR test was performed with the Coronex COVID-19 QPCR kit (DS BIO and NANO Tech. Ltd., Ankara, Turkey) as the standard method. Individuals with a positive RT-

PCR test result were accepted as COVID-19 patients. Patients were examined for the presence of COVID-19 symptoms including fever, cough, dyspnea, generalized pain, weakness, anorexia, nausea, vomiting, diarrhea, and anosmia and the findings were recorded. When thoracic computed tomography (CT) images were available, the presence of a ground-glass appearance or pneumonic infiltration on such images was recorded as a positive finding.

Patients with COVID-19 are considered severely ill if SpO2 is <94% in room air at sea level, respiratory rate is >30 breaths/min, PaO2/FiO2 is <300 mmHg, or lung infiltrates are >50% in room air at sea level. These patients may experience rapid clinical deterioration [5-7]. Critically ill patients may have ARDS, septic shock representing virus-induced shock of distribution, cardiac dysfunction, exaggerated inflammatory response, and/or exacerbation of underlying comorbidities [6, 7]. Venous blood samples obtained at admission were studied using the Sysmex XN-1000 modular system device (Sysmex Corp., Kobe, Japan). Of the complete blood count parameters, the white blood cell (WBC) count, hemoglobin levels, neutrophil and lymphocyte counts, and IG% were measured and the results were recorded. Of the biochemical parameters, venous blood gas levels, glomerular filtration rate (GFR), and levels of C-reactive protein (CRP), serum creatinine, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and glucose were assessed. Sociodemographic data and comorbid diseases were recorded. CKD patients included in the study were grouped into 5 categories as defined in the 2002 guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI) for the evaluation, classification, and stratification of CKD. According to these guidelines, category 1 refers to kidney damage with normal or increased GFR levels of ≥90 mL/min/1.73 m2, category 2 refers to kidney damage with a mild reduction in GFR characterized by GFR values in the range of 60-89 mL/min/1.73 m2, category 3 refers to moderate renal impairment characterized by GFR values in the range of 30-59 mL/min/1.73 m2, category 4 refers to severe renal failure characterized by GFR values in the range of 15-29 mL/min/1.73 m2, and category 5 refers to end-stage renal failure characterized by GFR values of <15 mL/min/1.73 m2. The standard treatment protocol administered to the patients was developed in accordance with the current recommendations specified in the treatment guidelines for adult patients issued by the Ministry of Health of the Republic of Turkey. The relationship of IG% with COVID-19 and in-hospital mortality was investigated, covering the prognostic processes. According to the occurrence of in-hospital mortality, the patients were categorized into groups and intergroup comparisons were performed.

Statistical Analysis

Standard deviation and mean values were calculated for continuous variables. Medians and interquartile ranges were calculated for non-parametric data. Each independent variable was compared between the groups by either the chi-square test or the independent t-test, whichever was suitable. Descriptive statistical analysis of all variables was carried out using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Logistic regression analysis was performed to investigate the factors associated with mortality. Statistical significance was defined at a p<0.05.

Results

Our study included 87 patients who met the inclusion criteria. Of these patients, 45 (51.7%) were men and 42 (48.3%) were women. The mean age of the patients was 67.07±13.52 years. Hypertension, diabetes, and coronary heart disease were the most common risk factors associated with the disease. The mean BUN level was 47.27±25.68 and the mean creatinine level was 2.94±2.14. The mean IG% value was 0.72±0.5. The patients were divided into two groups according to mortality. Of the patients included in the study, 71 (81.6%) were survivors and 16 (18.4%) were non-survivors. Non-survivors were older compared to survivors (73.06±9.91 vs. 65.72±13.91; p=0.021). There was a significant relationship between disease severity and mortality. The mortality rate was significantly higher in patients with severe or critical disease (p<0.001). The need for

mechanical ventilation was significantly higher in non-survivors (p<0.001). The comparison of the mean IG% values between the survivor and non-survivor groups did not reveal a significant correlation (0.72±0.52 vs. 0.71±0.42; p=0.754) (Figure 1). No significant differences were found in other parameters between the groups. The clinical characteristics of the patients included in the study are listed in Table 1.

Patients were classified into two groups as patients with lower (<0.6) and elevated (≥0.6) baseline IG% values. In the groups with normal and high baseline IG% values, there were 46 (52.8%) and 41 (47.2%) patients, respectively. There were no significant differences in age, gender, or disease-related risk factors between the groups with high and normal IG% levels. Furthermore, laboratory test results were not significantly different between these groups. The comparison of disease

Table 1. Characteristics and outcomes of patients with COVID-19

Variables	Total (n=87)	Survivors (n=71)	Non-survivors (n=16)	p
Age, years	67.07±13.52	65.72±13.91	73.06±9.91	0.021
Male gender, n (%)	45 (51.7)	36 (50.7)	9 (56.3)	0.688
Previous history, n (%)				
Hypertension	59 (67.8)	50 (70.4)	9 (56.3)	0.273
Diabetes mellitus	32 (36.8)	28 (39.4)	4 (25)	0.279
Cerebrovascular diseases	7 (8.0)	6 (8.5)	1 (6.3)	0.770
Coronary heart disease	26 (29.9)	19 (26.8)	7 (43.8)	0.180
Chronic pulmonary disease	4 (5.6)	0 (0)	4 (4.6)	0.331
Hyperlipemia	23 (26.4)	18 (25.4)	5 (31.3)	0.629
CKD stage				
Stage ≥4	57 (65.5)	44 (61.9)	13 (81.2)	0.335
Presence of acute kidney failure	23 (26.4)	18 (25.3)	5 (31.2)	0.629
Laboratory findings				
White blood cell count, ×103/mm3	7.60±3.41	7.15±2.85	9.59±4.85	0.126
Hemoglobin, mg/dL	11.41±2.48	11.35±2.31	11.64±3.21	0.751
Neutrophils, ×103/mm3	6.02±3.25	5.57±2.77	7.95±4.55	0.056
Lymphocytes, ×103/mm3	1.03±0.73	0.98±0.56	1.17±0.29	0.696
Glomerular filtration rate (IQR)	23 (25)	23 (28)	20 (13)	0.392
High-sensitivity CRP, ng/mL	99.25±10.65	96.54±11.41	99.05±19.28	0.570
Glucose, mg/dL	166.92±93.88	157.16±86.71	192.69±125.26	0.369
Blood urea nitrogen	47.27±25.68	44.59±21.56	44.08±13.61	0.872
Creatinine, mg/dL	2.94±2.14	2.73±2.03	3.51±2.84	0.375
Alanine transaminase, IU/L	38.11±7.19	34.88±7.42	36.54±9.92	0.731
Aspartate aminotransferase, IU/L	32.37±25.51	31.41±23.98	30.15±18.11	0.907
Total bilirubin, µmol/L (IQR)	0.5 (0.35)	0.5 (0.39)	0.5 (0.35)	0.521
Immature granulocytes (IG%)	0.72±0.5	0.72±0.52	0.71±0.42	0.754
Thorax computerized tomography (typical viral pneumonia sign)	72 (82.8)	59 (83.1)	13 (81.3)	0.860
Disease severity, n (%)				
Ordinary illness	67 (77)	64 (90.1)	3 (18.8)	<0.001
Severe or critical illness	20 (23)	7 (9.9)	13 (81.2)	<0.001
Administration of mechanical ventilation	15 (17.2)	3 (4.2)	12 (75)	<0.001

Table 2. Laboratory data of patients with COVID-19 on admission when grouped by immature granulocyte (IG%) values

Variables	Normal baseline IG% (n=46)	Elevated baseline IG% (n=41)	p
Age, years	65.74±14.51	68.56±12.33	0.354
Male gender, n (%)	26 (56.5)	19 (46.3)	0.343
Previous history, n (%)			
Hypertension	28 (60.9)	31 (75.6)	0.142
Diabetes mellitus	18 (39.1)	14 (34.1)	0.630
Cerebrovascular diseases	4 (8.7)	3 (7.3)	0.813
Coronary heart disease	16 (34.8)	10 (24.4)	0.290
Chronic pulmonary disease	3 (6.5)	1 (2.4)	0.364
Hyperlipemia	15 (32.6)	8 (19.5)	0.167
Laboratory findings			
White blood cell count, ×103/mm3	6.91±2.45	8.37±4.13	0.207
Hemoglobin, mg/dL	11.72±2.47	10.73±2.42	0.047
Neutrophils, ×103/mm3	5.22±2.17	6.92±3.98	0.120
Lymphocytes, ×103/mm3	1.15±0.84	0.90±0.57	0.167
Glomerular filtration rate (IQR)	26 (38)	21 (24)	0.443
High-sensitivity CRP, ng/mL	100.85±81.01	95.21±18.93	0.393
Glucose, mg/dL	134 (61)	143 (130)	0.291
Blood urea nitrogen	43.69±18.99	48.60±24.36	0.697
Creatinine, mg/dL	3.10±2.58	3.00±1.88	0.892
Alanine transaminase, IU/L	29.97±16.42	38.66±10.74	0.388
Aspartate aminotransferase, IU/L	33.18±19.69	28.20±22.97	0.220
Total bilirubin, µmol/L (IQR)	0.5 (0.41)	0.51 (0.31)	0.256
Thorax computerized tomography (typical viral pneumonia sign)	37 (80.4)	35 (85.4)	0.543
Disease severity, n (%)			
Ordinary illness	36 (78.3)	31 (75.6)	0.803
Severe or critical illness	10 (21.7)	10 (24.4)	0.769
Administration of mechanical ventilation	8 (17.4)	7 (17.1)	0.959

Table 3. Logistic regression analysis of the independent predictors of mortality

Variables	OR (95% CI)	p
Age	0.295 (0.075-1.152)	0.079
Blood urea nitrogen, mmol/L	1.125 (0.359-3.523)	0.840
High-sensitivity CRP, ng/mL	0.757 (0.212-2.706)	0.688
IG (%)	0.945 (0.311-2.874)	0.920

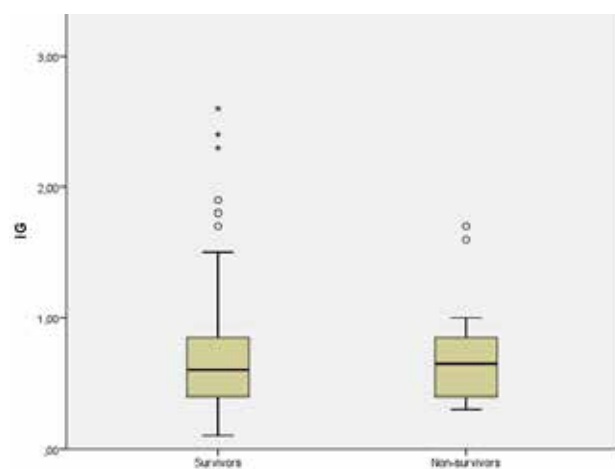IG%: Immature granulocyte percentage; CRP: C-reactive protein.

Figure 1. Box plot presentation of groups for immature granulocyte percentages.

severity between the groups with high and normal IG% levels did not reveal a significant difference (24.4% vs. 21.1%; p=0.769). In addition, high IG% values did not correlate with the need for mechanical ventilation for the management of the disease (p=0.959). The demographic, clinical, and laboratory data of the COVID-19 patients at admission are shown in Table 1 by IG% values. The results of the logistic regression analysis that was conducted to determine the factors that might act on mortality revealed that age [0.295 (0.075-1.152), p=0.079], BUN levels [1.125 (0.359-3.523), p=0.840], CRP levels [0.757 (0.212-2.706), p=0.688], and IG% [0.945 (0.311-2.874), p=0.920] were not associated with mortality (Table 3).

Discussion

COVID-19 is spreading rapidly around the world, contributing to the continued severity of the pandemic. Although many cases can be asymptomatic or present with only mild symptoms, COVID-19 can entail a wide range of clinical symptoms that might progress to severe and fatal pneumonia and multi-organ failure [11, 12]. Studies have shown that COVID-19 and chronic comorbidities such as advanced age, male gender, obesity, cardiovascular disease, diabetes, and kidney failure are associated with poor survival [5, 13]. In patients with COVID-19, it has been reported that there is a relationship between prognosis and acute phase reactants, including hematological parameters (WBC, platelet, and lymphocyte counts, etc.) and the levels of CRP, lactate dehydrogenase, ferritin, and D-dimer [14, 15]. In this study, we examined the prognostic value of IG% as an inflammatory marker for the first time in the literature to estimate prognosis in COVID-19 patients with CKD. We have found that IG% is not a marker of mortality in patients with CKD.

Although the underlying cause of the occurrence of infections with highly contagious SARS-CoV-2 has not been fully understood yet, the key role of inflammation in infectious diseases cannot be denied. Studies about the progression of viral pneumonia in COVID-19 have reported an increase in proinflammatory cytokines [16, 17]. The well-known inflammatory parameters include the counts of WBCs, neutrophils, lymphocytes, and platelets and their ratios, such as the NLR and PLR. Many

studies have shown that the use of such markers is feasible in the diagnosis, follow-up, and estimation of disease prognosis because the test results can be obtained quickly at low costs [18, 19]. In this study, we examined the association of IG% with mortality in COVID-19 patients with CKD as a marker that physicians are usually not familiar with.

It has been reported that hematological, biochemical, inflammatory, and immune biomarker abnormalities occur in patients with severe COVID-19 [20]. In a meta-analysis performed by Henry et al., it was found that the WBC count is elevated and lymphocyte and platelet counts are low in patients with severe COVID-19 [14]. Another study reported disorders in the immune response in COVID-19 patients and showed the relationship of disease severity with elevated leukocyte and low monocyte, eosinophil, and basophil counts [21]. IG% can be easily obtained via complete blood count as an easy-to-perform test available in any emergency department. Because IG% indicates bone marrow activation, it has been stated that it can possibly be used as an indicator of early-stage inflammation [8, 22]. Many studies have reported that IG% can be used in the diagnosis and estimation of prognosis in many diseases, especially in cardiovascular and gastrointestinal system diseases [23, 24]. In one study, it was shown that IG% could help predict the likelihood of early in acute appendicitis patients as a parameter that can be tested quickly without extra costs [25]. In a study of 301 patients with clinical findings of sepsis, Ayres et al. demonstrated that IG% of <2.0% helped exclude the diagnosis of sepsis with very high specificity and that IG% could be a useful additional adjunctive marker to diagnose sepsis and initiate early treatment [10]. Patients with CKD have increased risk for infections and infection-related mortality. The increased risk of infections is likely related to a dysregulated immune system. Infections are the second most common cause of death for dialysis patients, and some studies have found an annual death rate of several hundred times higher secondary to sepsis compared to the general population [21-25]. Therefore, the contribution of parameters such as IG%, which is associated with infection, to early intervention and treatment cannot be denied. To the best of our knowledge, there are no studies in the literature examining the relationship between IG% and mortality in CKD patients with COVID-19. Our results have shown that IG% is not a parameter that can be used to predict mortality in patients with CKD despite the elevated baseline values observed in approximately half of the patients.

Our study has some limitations. First, the study had a retrospective design and was conducted at a single center. Second, the time from the onset of symptoms to the time of emergency unit admission and the collection of blood samples could not be analyzed. We consider it a limitation that may have affected our results. In addition, only baseline IG% levels at admission could be tested; it was not possible to perform serial IG% measurements in the emergency room. Multi-center prospective studies with larger patient populations are needed to better interpret the findings of our study.

Conclusion

The results of our study have shown that IG% cannot be used as an indicator to predict mortality in CKD patients with COVID-19.

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